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HILL, KEVIN KAI	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/624,631	GRASSO ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,20,28 and 72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,20,28 and 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Amendments

Applicant's amendments to Claims 19 and 28, in the reply filed January 22, 2007, is acknowledged. Also acknowledged is Applicant's new claim, Claim 72, which has been entered into the application as requested and will be examined on the merits herein, as it is considered to belong to the elected group. Applicant has cancelled Claims 26, 44 and 67.

Claims 19-20, 28 and 72 are under consideration.

Drawings

1. **The drawings stand objected to as failing to comply with 37 CFR 1.84(p)(5)** because they do not include the following reference sign(s) mentioned in the description: page 9 of the specification discloses that Figure 4 consists of two panels, Panel A and Panel B. Similarly, page 24 of the specification discloses the contents illustrated in Figure 4, Panel A. However, Figure 4 as filed in the instant application, contains one panel that is neither labeled "Panel A" nor "Panel B". Furthermore, the numbered lanes in the instant Figure 4 panel are not disclosed in the specification, and thus the identity of the samples represented in each lane are unknown.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will

be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

In a telephone conversation with Applicant's representative, Mr. Cocca, on March 21, 2007, the Examiner informed Mr. Cocca of typographical errors regarding the annotation of paragraph numbers of the specification to be amended. It appears that ¶[0010] and [0011] in the amendment to the specification filed January 22, 2007 more correctly refer to the subject matter disclosed in ¶[0037] and [0038], respectively, as per the specification filed July 21, 2003. The subject matter of amended paragraphs addresses the instant objection to the drawings. It is the Examiner's understanding that a supplemental amendment will be submitted to correct this annotation error. Until such time, the instant objection remains standing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claims 19-20 and 28 stand and Claim 72 is newly rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of

ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-1111 (also available at www.uspto.gov).

The claimed invention is directed to a method for producing a high titer antibody producing cell comprising suppressing the expression of alpha-1-antitrypsin (AAT) and/or endothelial monocyte activating polypeptide I (EMAP).

The scope of the method encompasses *in vitro*, *ex vivo* and *in vivo* (page 26, [0078]) environments, even to the point of creating transgenic organisms (page 18, [0062]) to suppress the expression of alpha-1-antitrypsin (AAT) and/or endothelial monocyte activating polypeptide I (EMAP) genes, thus yielding a high titer antibody producing cell. Similarly, the scope of the alpha-1-antitrypsin (AAT) genes and/or endothelial monocyte activating polypeptide I (EMAP) genes to effect high-titer antibody producing cells (page 7, [0022]) embraces a genus of structurally and functionally diverse genes. The preferred embodiment of the instantly elected invention, Claim 28, is to introduce into the cell a knock-out targeting vector to disrupt the function of genes encoding alpha-1-antitrypsin (AAT) and/or endothelial monocyte activating polypeptide I (EMAP).

The scope of the method of "suppressing" encompasses intracellular and extracellular administration of structurally and materially diverse compositions that have distinctly different modes of operation to directly or indirectly affect the expression, that is increase or decrease, of at least one gene involved in antibody production. When the claims are analyzed in light of the specification, the inventive concept of the instant application is to administer dominant-negative molecules, antisense molecules, ribozymes, knock-out targeting vectors, catalytic antibodies, polypeptide inhibitors, intracellular and/or extracellular antibodies, pharmacologic saturation of substrates or ligands, and molecules of biological or chemical basis that can affect the gene expression profile (page 4, [0012-0013]; page 7, [0022]) to modulate the expression of a gene

involved in antibody production. The preferred embodiment of the instantly elected invention, Claim 28, is to suppress the expression of said gene(s) by introducing into the cell a knock-out targeting vector to disrupt the function of said gene(s).

The scope of high titer antibody producing cells encompasses diverse organisms across the prokaryotic and eukaryotic kingdoms, wherein Applicant has contemplated bacteria, yeast, plants and mammals, for example (page 4, [0010]). The preferred embodiment of the instantly elected invention is a hybridoma cell (Claim 20) and a rodent cell (Claim 72).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. However, the specification does not teach what is the complete structure of any species of the genus of targeting vectors by which the AAT and/or EMAP gene(s) is(are) knocked-out. Rather, the specification discloses the cooperative use of an expression vector encoding a structurally undefined antisense molecule directed against the AAT gene of SEQ ID NO: 1 and an expression vector encoding a structurally undefined antisense molecule directed against the EMAP gene of SEQ ID NO:2 in the H6 hybridoma cell line (page 23, [0072]).

The art recognizes (Doetschman, 1999) that knock-out targeting vectors require the presence of DNA sequences homologous to the target gene and flanking the disrupted gene cassette to facilitate homologous recombination into the targeted genome, thus replacing the endogenous gene with an exogenous gene fragment and thereby altering the endogenous gene in a pre-specified manner. The art also recognizes (Forsyth et al, 2003) that alpha-1-antitrypsin (AAT) is a member of the rather large family of serine protease inhibitors (SERPINs) and that, in striking contrast to the human and bovine genomes wherein AAT is represented by a single gene, individual mouse species possess as many as five AAT genes (page 337, column 2). For example, the *M. domesticus* C57/BL/6J, AJ, and C3H/HeJ laboratory strains express five AAT genes; whereas, the *M. domesticus* AKR/J and DBA/2J laboratory strains express only three AAT genes. The art also recognizes that the term "hybridoma", as commonly used in the art, represents antibody producing B-cells fused with immortalized myeloma cells, wherein the mammalian species of the B-cells and the mammalian species of the myeloma cells need not be identical, to produce a rapidly and indefinitely growing population of hybridoma cells that will

produce antibodies, wherein each specific hybridoma fusion will produce one type of antibody. The specification does not disclose the species derivation of the H6 hybridoma cell, but for example, Komori et al, (1988) teach a human-mouse hybridoma (H6-3C4). The specification does not provide any disclosure regarding the number of existing mammalian AAT genes expressed within the H6 hybridoma cell line.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that the knock-out targeting vector would disrupt the function of the AAT gene(s) and/or EMAP gene(s). **In regard to a DNA knock-out vector that can disrupt the gene expression of AAT of SEQ ID NO:1 and EMAP of SEQ ID NO:2 from mice, it is noted that the specification does not provide any disclosure regarding whether the knock-out vector would have had the same characteristics and properties or would have had additional characteristics and properties on the other AAT and EMAP genes present in the hybridoma and any other possible mammalian genomes of the hybridoma cell.** The specification does not provide any disclosure regarding the structural nature of the AAT and/or EMAP knock-out vector, nor any guidance as to whether or not this structurally undisclosed knock-out construct inactivates all of the existing mammalian AAT and EMAP genes expressed within the H6 hybridoma cell line.

The method of Claim 28 is drawn to a knock-out targeting vector to disrupt the function of genes encoding alpha-1-antitrypsin (AAT) and/or endothelial monocyte activating polypeptide I (EMAP). The specification does not disclose any identifying characteristic as to how an artisan would have differentiated one DNA knock-out vector requiring homologous recombination into a host cell AAT gene from any other DNA knock-out vector requiring homologous recombination into other AAT genes. Similarly, the specification does not disclose any identifying characteristic as to how an artisan would have differentiated one DNA knock-out vector requiring homologous recombination into a host cell EMAP gene from any other DNA knock-out vector requiring homologous recombination into a host cell EMAP gene. Similarly, the specification does not disclose any identifying characteristic as to how an artisan would have differentiated one DNA knock-out vector requiring homologous recombination into a host cell

AAT or EMAP gene from any other DNA knock-out vector requiring homologous recombination into a host cell to disrupt both AAT and EMAP genes. Furthermore, given the art recognized genus of AAT genes, the specification does not disclose how an artisan would have knocked-out all AAT genes in the hybridoma cell. It is noted that all these knock-out targeting vectors directed to their respective AAT gene(s) vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

The Revised Interim Guidelines state, "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus .....In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Further, *Vas-cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-cath* at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200,

1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

The applicant has not provided any description or reduction to practice of introducing a knock-out targeting vector, as commonly understood in the art, to disrupt an endogenous gene(s) encoding AAT and/or EMAP obtained through homologous recombination between a targeting construct encoding two portions of SEQ ID NO:1 and/or SEQ ID NO:2 flanking a marker gene such that insertion of the marker gene into endogenous SEQ ID NO:1 and/or SEQ ID NO:2 results in loss of endogenous AAT and/or EMAP gene expression. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the nucleotide sequences which encode AAT and/or EMAP as defined by the specification or the detailed chemical structure of the genus of disruptions of AAT and/or EMAP sequences encompassed by the claims. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the necessary starting materials, that is a knock-out targeting vector to disrupt the function of the alpha-1-antitrypsin genes and/or the endothelial monocyte activating polypeptide I gene(s), to perform the necessary active steps and effect the claimed method at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus. Thus, for the reasons outlined above, Claims 19-20, 28 and 72 do not meet the requirements for written description under 35 U.S.C. 112, first paragraph.

Applicant's Arguments

Applicant argues that:

a) the disclosure demonstrates that at least one of gene in each of the AAT and EMAP families, when suppressed, enhances antibody expression, to support the encompassed genus. Those of skill in the art would understand that Applicants are in possession of

those particular members of the AAT and/or EMAP gene family that enhance antibody expression upon their respective suppression,

b) the particular AAT and EMAP genes can be suppressed according to the inventive methods, and

c) Applicants submit that the information provided by the instant disclosure, coupled with the broad knowledge of knock out technology established in the art, provides sufficient structure (AAT and EMAP genes) and function (knockout) to inform those of skill in the art that the Applicants were in possession of the full scope of the invention as claimed.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), the functional limitation of enhancing antibody expression does not support the breadth of the claimed AAT and EMAP genera, respectively. The art is silent with respect to the function of each of the numerous AAT and EMAP genes extant in the enormous genus of organisms encompassed by the claims. Applicant has provided no evidence that the other genes of the AAT gene family, for example, have any biological function or relevance regarding antibody synthesis, so as to make up for this deficiency as it pertains to antibody production.

With respect to b), that a phenotype is observed in one particular cell type using particular antisense oligonucleotides directed to particular AAT and EMAP genes is not contested. The substantive issue is whether the claimed method, specifically genomic knock-out technology, would result in the same phenotype in the enormous genus of cell types embraced by the claims. As discussed in the enablement rejection below, the art does not teach predictability using antisense oligonucleotides, nor in gene knock-out transgenic animals. Furthermore, Applicant has not provided evidence to demonstrate that genomic eradication of the particular AAT and EMAP alleles yield the claimed phenotype. Thus, the particular method, antisense oligonucleotides, applied to the particular alleles, AAT of SEQ ID NO:1 and EMAP of SEQ ID NO:2, in hybridoma cells does not reasonably represent the breadth of the claimed genera of genes in the claimed genus of cell types as per gene knock-out. Furthermore, the claims recite the use of a single knock-out vector to inactivate a plurality of genes. There is no evidence that such a knock-out vector inactivating a plurality of genes has been made, and thus it naturally follows

that no evidence is provided disclosing a transgenic cell whose genome comprises said knock-out vector inactivating a plurality of genes.

With respect to c), MPEP §2163.02, Standard for Determining Compliance with the Written Description Requirement: "Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

The specification does not disclose, and the instant amendment provides no evidence of, the knock-out targeting vector to disrupt the function of AAT and/or EMAP genes in any cell so as to yield the claimed phenotype. The disclosure that knock-out vectors are known in the art and that an artisan may design a gene-specific vector(s) based upon the known structures of AAT and EMAP genes is not sufficient to demonstrate possession of the claimed invention because the art recognizes significant unpredictability in the generation of a desired phenotype when knocking out target gene(s). This unpredictability is enhanced by the lack of knowledge in the art regarding the instant genes, and their related family members, encompassed by the claims. Applicant has provided no evidence that the invention was "ready for patenting" to show the

invention was complete, specifically a transgenic cell in which a specific AAT gene is knocked out and/or a specific EMAP gene is knocked out so as to yield increase production of antibodies.

3. **Claims 19-20 and 28 stand and Claim 72 is newly rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claimed invention is directed to a method for producing a high titer antibody producing cell comprising modulating the expression of at least one gene involved in antibody production.

The scope of the method can be reasonably interpreted to encompass *in vitro*, *ex vivo* and *in vivo* environments in which the expression of at least one gene involved in antibody production is modulated to produce a high titer antibody producing cell. When the claims are analyzed in light of the specification, the inventive concept of the instant application encompasses method(s) performed *in vitro*, *ex vivo* and *in vivo* (page 26, [0078]), even to create transgenic organisms (page 18, [0062]). The preferred embodiment of the instantly elected invention performs the method *in vitro*.

The scope of the method of "suppressing" can be reasonably interpreted to encompass diverse environmental conditions, including temperature and atmospheric variables, and the intracellular and extracellular administration of structurally and materially diverse compositions that have distinctly different modes of operation to directly or indirectly affect the expression, that is decrease, of alpha-1-antitrypsin (AAT) gene expression and/or function and/or endothelial monocyte activating polypeptide I (EMAP) gene involved in antibody production. When the claims are analyzed in light of the specification, the inventive concept of the instant application is to administer dominant-negative molecules, antisense molecules, ribozymes, knock-out targeting vectors, catalytic antibodies, polypeptide inhibitors, intracellular and/or extracellular antibodies, pharmacologic saturation of substrates or ligands, and molecules of biological or chemical basis that can affect the gene expression profile (page 4, [0012-0013]; page 7, [0022]) to modulate the expression of a gene involved in antibody production. The preferred embodiment of the instantly elected invention, Claim 28, is to suppress the expression of said gene(s) by introducing into the cell a knock-out targeting vector to disrupt the function of said gene(s).

The inventive concept of the instant application is to inhibit or disrupt the expression of alpha-1-antitrypsin (AAT) gene expression and/or function and/or endothelial monocyte activating polypeptide I (EMAP) gene expression and/or function to effect high-titer antibody producing cells (page 7, [0022]). The preferred embodiment of the instantly elected invention, Claim 28, is to introduce into the cell a knock-out targeting vector to disrupt the function of genes encoding alpha-1-antitrypsin (AAT) and/or endothelial monocyte activating polypeptide I (EMAP).

The scope of high titer antibody producing cells encompasses diverse organisms across the prokaryotic and eukaryotic kingdoms, as Applicant has contemplated bacteria, yeast, plants

and mammals, for example (page 4, [0010]). The preferred embodiment of the instantly elected invention is a hybridoma cell (Claim 20) and a rodent cell (Claim 72). It is unclear how the instantly claimed method, specifically using gene knock-out technology, may be performed in cell types that, by definition, do not encode AAT or EMAP genes, e.g. bacteria and yeast, for example.

The State of the Prior Art, The Level of One of Ordinary Skill, and The Level of Predictability in the Art

The art teaches (Forsyth et al, 2003) that alpha-1-antitrypsin (AAT), also known as alpha-1-protease inhibitor, is a member of the rather large (>700 known to date) and functionally diverse family of serine protease inhibitors (SERPINs). Forsyth et al teach that, in striking contrast to the human and bovine genomes wherein AAT is represented by a single gene, four genes are found in the guinea pig and rabbit and individual mouse species possess as many as five AAT genes (page 337, column 2). Furthermore, intraspecific gene number variation is observed, as the *M. domesticus* C57/BL/6J, AJ, and C3H/HeJ laboratory strains express five AAT variants; whereas, the *M. domesticus* AKR/J and DBA/2J laboratory strains express only three AAT variants. Each member of the AAT gene family shares the strongly conserved, protease recognition region that is exposed for interaction with the AAT ligand. Thus, numerous AAT genes exist in the disclosed H6 hybridoma cell line, including other mammalian AAT gene(s), the Applicant-disclosed murine AAT gene of SEQ ID NO:1, and at least two and potentially four, additional ATT murine genes.

The art also teaches that hybridoma technology for the production of antibodies for both research and therapeutic purposes has been in use for almost thirty years, and thus the level of ordinary skill in the art is high (Laffly and Sodoyer, 2005). Laffly and Sodoyer recognize that "the huge demand for large amounts of monoclonal antibodies is currently driving improvement of existing expression systems or the quest for alternative production means" (page 45, column 2, lines 4-7). The art recognizes that the term "hybridoma", as commonly used in the art, represents antibody producing B-cells fused with immortalized myeloma cells, wherein the mammalian species of the B-cells and the mammalian species of the myeloma cells need not be

identical, to produce a rapidly and indefinitely growing population of hybridoma cells that will produce antibodies, wherein each specific hybridoma fusion will produce one type of antibody. The specification does not disclose the species derivation of the H6 hybridoma cell; however, Komori et al (1988), for example, teach a human-mouse hybridoma (H6-3C4). The specification does not provide any disclosure regarding the number of existing mammalian AAT genes expressed within the H6 hybridoma cell line.

With respect to any effect alpha-1-antitrypsin (AAT) activity contributes towards antibody production, the art is largely silent. Jeanin et al teach that exogenously applied AAT potentiates IgE and IgG4 synthesis in human peripheral blood morphonuclear cells (PBMCs) and B-cells, resulting in a 950% increase in IgE production (see Figures 1-3 and Table 1). In contrast to the *trans*-effect taught by Jeanin et al, the art makes no mention of any *cis*-effect AAT expression, or lack thereof, contributes towards antibody production within the given host cell wherein AAT gene expression has been abrogated, down-regulated or disrupted entirely. Rather, the art teaches that the build-up of improperly folded AAT contributes to human disease by impairing protein maturation in the endoplasmic reticulum, polymerizing into protein aggregates and forming intracellular inclusion bodies, and ultimately causing cytotoxicity (Welch et al, 2004). Thus, complete removal of the alpha-1-antitrypsin (AAT) gene(s) in any organism for the production of high-titer antibody producing cells, as disclosed in the specification, is not a routine practice, and despite the general high level of expertise in the art, considerable unpredictability exists in the field regarding any effect AAT has on antibody production and secretion, especially in light of the organism-dependent diversity of AAT gene number.

At the time of filing, the art did not consider the phenotype of a knock-out to be predictable. The art teaches that while the promise of gene targeting had been to reveal the *in vivo* function of a gene of interest, the functional relevance of gene targeting has been questioned because the mutation might lead to an avalanche of compensatory processes (up- or down-regulation of gene products) and resulting secondary phenotypical changes. The art recognizes (Doetschman, 1999) that knock-out targeting vectors require the presence of DNA sequences homologous to the target gene and flanking the disrupted gene cassette to facilitate homologous

recombination into the targeted genome, thus replacing the endogenous gene with an exogenous gene fragment and thereby altering the endogenous gene in a pre-specified manner. Doetschmann provides numerous examples of instances in which genes considered well-characterized *in vitro* have produced unexpected phenotypes or indiscernible or no phenotypes in transgenic or knockout mice. Moens et al (1993, Development, 119: 485-499) further teach that different mutations in the same gene can lead to unexpected differences in the phenotype observed. Moens et al. shows that two mutations produced by homologous recombination in two different locations of the *N-myc* gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null. A null mutant organism might not only lack the product of a single gene, but might also possess a number of physiological or other processes that have been altered to compensate for the effect of the null mutation (Gerlai, 1996, Trends Neurosci, 19: 177-181, page 177, column 1, paragraph 1). Gerlai teaches an example wherein background genotype can confound the exhibited phenotypes. Targeted disruption of a gene of interest, Gene 1, might lead to changes in expression of alleles b and B for Gene 2. A regulatory change in Gene 2 might lead to different phenotypic changes, depending on which allele (b or B) is present in the organism with the null mutation in Gene 1. The consequences of this problem is that due to this polymorphism in the genetic background, one cannot conclude for certain that a phenotypic change exhibited in a null-mutant resulted from the null mutation or to the genetic background (Gerlai, page 177, column 1, under "Polymorphism in the genetic background might make the results of gene-targeting studies difficult to interpret").

Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of transgenic or knockout conditions even when the activity of the gene has been extensively studied *in vitro*. With respect to the instant invention, Gerlai's teachings indicate that an artisan cannot predict that any gene disruption would necessarily result in a phenotype. And if a phenotype were to result, an artisan cannot predict that the resultant phenotype was the result of the gene disruption. The teachings by Gerlai indicate that phenotypes exhibited by knock-out transgenes can be the result of unrelated factors. The teachings in the art indicate that guidance needs to be given such than an artisan knows how to discriminate what phenotypes are the result of AAT and/or EMAP gene disruption(s) and what are the result of non-specific factors such as genetic background. Given that alpha-1-antitrypsin (AAT) is a member of the rather large genus

of serine protease inhibitors (SERPINS) that have a variety of diverse functions in the animal, an artisan cannot predict what biological function occurs in a family of SERPINS such that an artisan would know that the phenotype exhibited in the knockout cell or organism is a result of the gene disruption. The artisan cannot reasonably predict that the phenotype is the result of gene disruption, because the art teaches that non-specific factors, such as genetic background, affect the presence or absence of phenotypes. As such, the specification fails to teach that the phenotypes have a biological relationship with AAT and/or EMAP gene disruption.

With regard to the ability of an artisan to correlate an observed antisense RNA phenotype to a predicted phenotype using targeting vectors that knock-out a targeted gene, Caplen teaches that the RNAi machinery can be saturated, so there will probably be a limit to the number of different genes that can be targeted in a cell at one time (page 1244, column 1). Furthermore, Caplen expresses the importance in recognizing that there is variation in the degree of inhibition mediated by different small interfering RNA sequences which may result in the production of different phenotypes. Thus, the disclosure of a phenotype in response to the expression of a single, structurally undefined antisense molecule (page 24, Example 4, Table 2, discussed below) cannot reasonably predict the phenotype obtained when the individual gene is totally disrupted.

The Amount of Direction Provided by the Inventor and The Existence of Working Examples

The inventive concept of the instant application is a method to inhibit or disrupt the function of alpha-1-antitrypsin (AAT) and/or endothelial monocyte activating polypeptide I (EMAP) genes to effect high-titer antibody producing cells (page 7, [0022]). The preferred embodiment of the instantly elected invention, Claim 28, is a method to suppress the expression of said gene(s) by introducing into the cell a knock-out targeting vector to disrupt the function of said gene(s). Given the absence in the prior art teaching a mechanism linking AAT expression/activity and antibody production, an artisan is dependent upon the instant disclosure to provide specific, not general, guidance.

With regard to the method for enhancing antibody production in a hybridoma cell by introducing a knock-out vector into the cell to inactivate expression of genes encoding AAT and/or EMAP, the specification does not teach an example of the claimed method. Rather, the specification teaches that the H6 hybridoma cell line containing vectors expressing structurally

unknown antisense constructs to both the alpha-1-antitrypsin (AAT) gene of SEQ ID NO:1 and the endothelial monocyte-activating polypeptide I (EMAP) gene of SEQ ID NO:2 (page 24, Example 4, Table 2). However, given the absence of a structural disclosure identifying the specific chemical nature of these antisense constructs, the degree of unpredictability in the art regarding antisense RNA methods to decrease the expression of one's gene(s) of interest, the fundamental nature of numerous AAT genes existing in the hybridoma cell, and the novelty of the observed cellular response, one of ordinary skill in the art cannot reasonably predict the phenotype obtained when the individual gene(s) is(are) totally disrupted. Furthermore, method Claim 28 recites "*a* (*emphasis added*) knock-out targeting vector" and the specification does not provide specific active steps to guide an artisan to effectively inactivate all mammalian AAT genes by homologous recombination with one knock-out targeting vector.

With regard to the method for enhancing antibody production in cells associated with hypoimmunoglobulin disease, the specification does not provide an example of introducing a knock-out vector in any cell type associated with hypoimmunoglobulin disease of any organism to inactivate a specific AAT gene(s) to enhance antibody production.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Therefore, in view of the art recognized diversity in species-specific AAT gene number(s), the silence in the art teaching any role(s) any alpha-1 antitrypsin activity has on antibody production, the breadth of the AAT genes and disruptions in the AAT and/or EMAP genes claimed, the lack of specific demonstrations in the disclosure teaching method steps of introducing a targeting vector to disrupt the genes encoding any AAT, alone or in combination with, EMAP that will cause increased antibody production, the lack of a null phenotype resulting in high titer antibody production observed by the prior art when AAT and/or EMAP genes are knocked-out in cells or organisms, the unpredictability in determining a knock-out phenotype even when the activity of the gene has been *extensively* (*emphasis added*) studied *in vitro*, the unpredictability in correlating any observed phenotype in a knockout cell or organism with gene disruption as acknowledged by the prior art, and the etiological and pathological diversity of hypoimmunoglobulin disease origins, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the

specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the method step of introducing a knock-out targeting vector to inactivate any alpha-1-antitrypsin gene(s), alone or in combination with, endothelial monocyte activating polypeptide I gene(s) in a cell will result in a high-titer antibody producing cell or enhance antibody production in a cell associated with hypoimmunoglobulin disease.

The lack of written support in the specification regarding the necessary starting materials required to perform the preferred embodiment of the instantly elected method invention, Claim 28, to suppress the expression of genes encoding alpha-1-antitrypsin (AAT) and/or endothelial monocyte activating polypeptide I (EMAP) by introducing into a cell *a* (*emphasis added*) knock-out targeting vector to disrupt the function of said gene(s), has been addressed above.

However, as explained above, because the scope of the method of "modulating" can be reasonably interpreted to encompass diverse environmental conditions, including temperature and atmospheric variables, and the intracellular and extracellular administration of structurally and materially diverse compositions, as contemplated by Applicant (page 4, [0012-0013]; page 7, [0022]), that have distinctly different modes of operation to directly or indirectly affect the expression of "at least one gene involved in antibody production", prior art will be applied subsequently.

Applicant's Arguments

Applicant argues that it is not undue experimentation to suppress AAT or EMAP genes, to determine if suppression of a given AAT or EMAP gene results in enhanced antibody expression, and to screen cells transformed with knock out vectors for enhanced antibody expression.

Applicant's argument(s) has been fully considered, but is not persuasive.
The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the...noted factual considerations, specifically the breadth of the claims, the

nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404.

MPEP §2164.06(b) Decision Ruling that the Disclosure was Nonenabling

(A) In *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999), the court held that claims in two patents directed to genetic antisense technology (which aims to control gene expression in a particular organism), were invalid because the breadth of enablement was not commensurate in scope with the claims. Both specifications disclosed applying antisense technology in regulating three genes in *E. coli*. Despite the limited disclosures, the specifications asserted that the "[t]he practices of this invention are generally applicable with respect to any organism containing genetic material which is capable of being expressed ... such as bacteria, yeast, and other cellular organisms." The claims of the patents encompassed application of antisense methodology in a broad range of organisms. Ultimately, the court relied on the fact that (1) the amount of direction presented and the number of working examples provided in the specification were very narrow compared to the wide breadth of the claims at issue, (2) antisense gene technology was highly unpredictable, and (3) the amount of experimentation required to adapt the practice of creating antisense DNA from *E. coli* to other types of cells was quite high, especially in light of the record, which included notable examples of the inventor's own failures to control the expression of other genes in *E. coli* and other types of cells. Thus, the teachings set forth in the specification provided no more than a "plan" or "invitation" for those of skill in the art to experiment using the technology in other types of cells.

As discussed above, the single working example disclosed in the specification using a structurally undisclosed antisense nucleic acid applied to a single cell type does not reasonably extrapolate to genomic knock-out conditions applied to an enormous genus of cell types because the art recognizes that both antisense technologies and gene knock-out technologies are unpredictable. Furthermore, the art recognizes variation in the number of AAT genes encoded in the respective genomes of diverse organisms, and thus issues regarding potential functional redundancy must be addressed by the instant disclosure because the art is silent with respect to the claimed phenotypes attributed to the decreased expression of the particular alleles. The

simple statements advanced by Applicant that no undue experimentation exists is inadequate as compared to the novelty of the claimed invention, the silence in the art regarding the correspondence between the claimed genes and the disclosed biological activity with respect to antibody production, and the recognized unpredictability in the art regarding gene knock-out technologies as applied to the enormous genus of diverse cell types encompassed by the claims. Applicant has provided no evidence to demonstrate the use of the claimed invention.

Claim Rejections - 35 USC § 112

4. **The prior rejection** of **Claims 19, 26 and 44 under 35 U.S.C. 112, second paragraph is withdrawn** because Applicant has either cancelled or amended the claim to address the relevant issue(s).

Claim Rejections - 35 USC § 102

5. **The prior rejection of Claims 19-20 under 35 U.S.C. 102(b) is withdrawn** because Applicant has either cancelled or amended the claim to address the relevant issue(s).

Conclusion

6. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kevin K. Hill

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PRIMARY EXAMINER